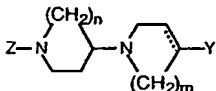




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(54) Title: ANTIDEPRESSANT HETEROCYCLIC COMPOUNDS <div style="text-align: center;"> (I)</div> (57) Abstract <p>Compounds of formula (I) are useful antidepressant agents demonstrating potent inhibition of 5-HT reuptake. Z is selected from among various phenyl and hetaryl moieties while Y is benzyl or indolyl.</p>		

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ANTIDEPRESSANT HETEROCYCLIC COMPOUNDS

Cross Reference to Related Application

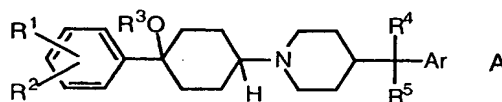
This non-provisional application claims priority from provisional application USSN 60/117,651 filed January 28, 1999.

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Background of the Invention

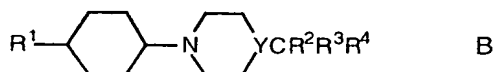
This invention pertains to cyclic amino compounds having antidepressant and other psychotropic, bio-affecting properties and to their preparation and use. In some preferred embodiments, the invention is concerned with 1,3-disubstituted pyrrolidine, 1,4-disubstituted piperidine, or
 10 1,4-disubstituted hexahydroazepine derivatives wherein the 3- or 4-substituent is benzyl, substituted benzyl, or substituted indolyl, and the 1-substituent is a 1-aryl-pyrrolidin-3-yl, 1-aryl-piperidin-4-yl, or a 1-aryl-hexahydroazepin-4-yl moiety. These compounds and others structurally related thereto possess a unique serotonergic profile that makes them useful
 15 in the treatment of depression.

Mattson and Catt disclosed a series of piperazinyl- and piperidinyl-cyclohexanols characterized by structural formula A as anxiolytic agents in U.S. Patent 5,387,593.



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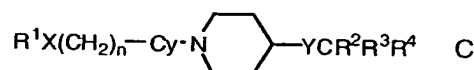
Mattson and Catt also disclosed a series of cyclohexylpiperazines and -piperidines characterized by structural formula B as antiischemic agents in U.S. Patent 5,352,678.



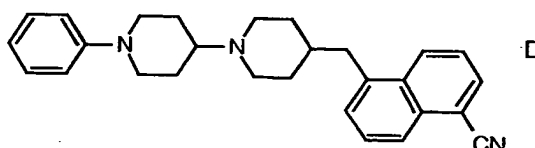
Mattson and Catt have also disclosed a series of piperazinyl- and
 25 piperidinyl-cyclohexenes and cyclohexanes characterized by structural

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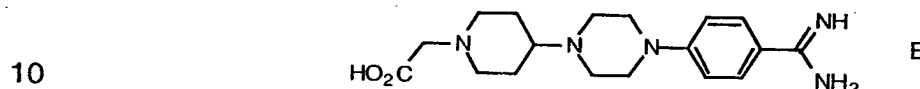
formula C for treating ischemia-induced brain disorders in Eur. Pat. Appl., 560669, September 15, 1993.



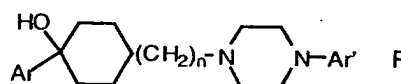
5 Scherer, et al. have disclosed the synthesis of some piperidinyloxy-piperidines, formula D, as fluorescent probes (Recl. Trav. Chim. Pays-Bas, 112(10), 535-48, 1993).



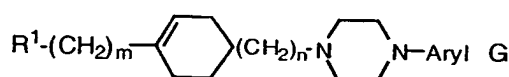
Eldred, et al. disclosed a series of antithrombotic agents characterized by the formula E in Journal of Medicinal Chemistry, Vol 37, pp 3882-5, 1994.



Caprathe, et al. disclosed a series of piperazinyloxy-cyclohexanol compounds characterized by structural formula F in U.S. Patent 4,957,921. Formula F is:

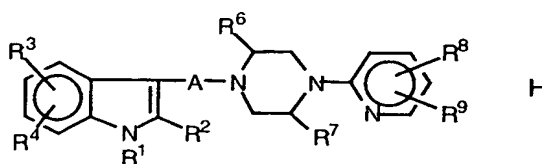


15 Caprathe, et al. disclosed a series of piperazinyloxy-cyclohexene compounds characterized by structural formula G in U.S. Patent 4,975,445. Formula G is:



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Smith, *et al.* in U.S. Patent 4,954,502 disclosed a series of compounds of structural formula H having antidepressant properties. In these compounds A was, *inter alia*, a 5 to 7 carbon cycloalkanyl or cycloalkenyl ring.

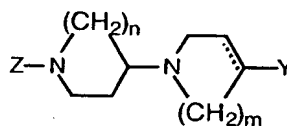


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Summary and Description of the Invention

In its broadest aspect, the invention is concerned with certain compounds which are substituted-benzyl or substituted-indolyl cyclic amino-substituted N-aryl or heteroaryl cyclic amines that are useful for treating CNS disorders such as depression. The compounds conform to formula I:

10



I

as well as pharmaceutically acceptable acid addition salts and/or hydrates thereof.

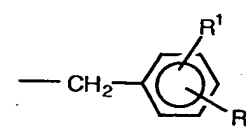
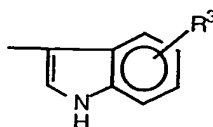
In formula I, Z is an aryl or hetaryl moiety selected from among phenyl, benzodioxane, benzodioxole, benzothiazole, pyridine, pyridazine, pyrimidine, and quinoline systems. These aryl or hetaryl rings can be unsubstituted or substituted with from one to three substituent groups selected from among C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano and halo.

15

The solid and dotted lines in formula I denote a double or a single carbon-carbon covalent bond. The symbols m and n are independently selected from the integers 1 to 3.

20

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Y can be  or , in which R¹ and R² are independently selected from hydrogen, halogen, or alkoxy; and R³ can be hydrogen, halogen or cyano.

5 Halo or halogen refers to fluoride, chloride, bromide or iodide substituents with fluoride, chloride and bromide preferred.

Additionally, compounds of formula I also encompass all pharmaceutically acceptable acid addition salts and/or solvates thereof. The present invention is also considered to include stereoisomers including geometric as well as optical isomers, e.g. mixtures of enantiomers as well as
10 individual enantiomers and diastereomers, which arise as a consequence or structural asymmetry in certain compounds of the instant series. Separation of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

The term "C₁₋₄" refers to both straight and branched chain carbon radicals of from 1 to 4 carbon atoms inclusive. Illustrative of these radicals
15 are carbon chains which can be methyl, ethyl, propyl, isopropyl, 1-butyl, 1-methylpropyl, 2-methylpropyl.

As can be seen, the formula I compounds comprise two sub-classes of compounds: 1) Y is a benzyl moiety and 2) Y is an indolyl moiety. Some
20 preferred compounds are shown below.

Preferred compounds (INDOLE CMPDS):

1-{4-[4-(5-fluoroindol-3-yl)piperidyl]piperidyl}-2,4-dimethoxybenzene;

3-[1-(1-(2H,3H-benzo[3,4-3]1,4-dioxan-6-yl)-4-piperidyl)4-piperidyl]indole-5-carbonitrile;

25 3-{1-[1-(2,4-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;

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3-[1-(1-(5-quinolyl)-4-piperidyl)-4-piperidyl]indole-5-carbonitrile;

3-{1-[1-(2-methylbenzothiazol-5-yl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;

3-{1-[1-(2,6-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile.

5 Preferred compounds (BENZYL CMPDS):

5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2H-benzo[d]1,3-dioxolane;

5-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) quinoline;

10 3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) benzenecarbonitrile;

2-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) pyrimidine;

2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-2,6-dimethoxybenzene;

3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl} piperidyl)-6-chloropyridazine;

15 1-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;

1-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;

20 1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;

2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-1,3,5-trimethoxybenzene;

5-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;

-6-

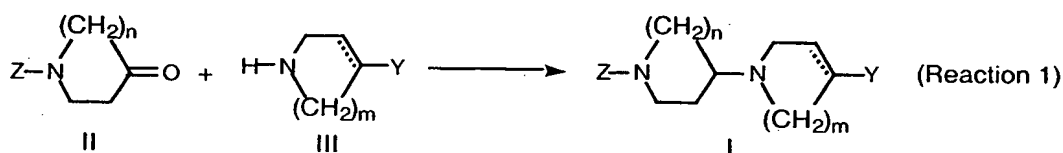
- 5-(4-{4-[(2-chlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5 5-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 3-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;
- 4-methoxy-3-(4-{4-[(3-methoxyphenyl)methyl]piperidyl}piperidyl)benzenecarbonitrile;
- 10 3-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;
- 1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2,4,5-trimethoxybenzene;
- 8-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-7-methoxy-2H,3H,4H-
15 benzo[b]1,5-dioxepin.

The pharmaceutically acceptable acid addition salts of the invention are those in which the counter ion does not contribute significantly to the toxicity or pharmacological activity of the salt and, as such, they are the pharmacological equivalents of the bases of formula I. They are generally preferred for medical usage. In some instances, they have physical properties which makes them more desirable for pharmaceutical formulation such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substance may be used for pharmaceutical purposes. The salts are routinely made by admixture of a Formula I base with the selected acid, preferably by contact in solution employing an excess of commonly used inert solvents such as water, ether, benzene, methanol, ethanol, ethyl acetate and acetonitrile.

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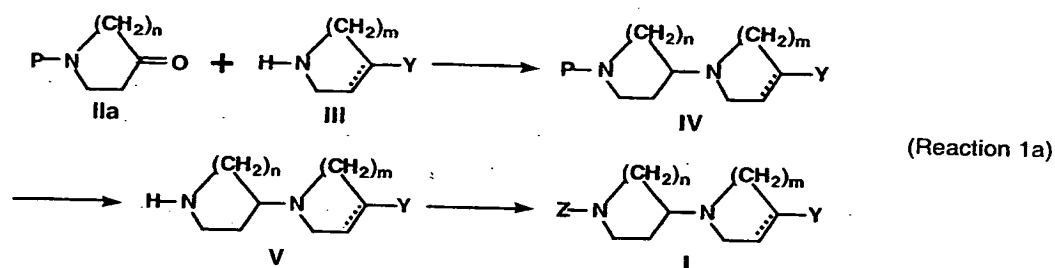
They may also be made by metathesis or treatment with an ion exchange resin under conditions in which the anion of one salt of the substance of the Formula I is replaced by another anion under conditions which allow for separation of the desired species such as by precipitation from solution or extraction into a solvent, or elution from or retention on an ion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation of the substances of Formula I include sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, cinnamic, fumaric, mandelic, phosphoric, nitric, mucic, isethionic, palmitic, heptanoic, and others.

- Compounds of formula I are most conveniently synthesized by the coupling (Reaction 1) of intermediates II and III under reductive alkylation conditions such as, titanium isopropoxide/ NaBH_4 , sodium cyanoborohydride, sodium triacetoxyborohydride and the like. Other methods known to those skilled in the art may also be used.



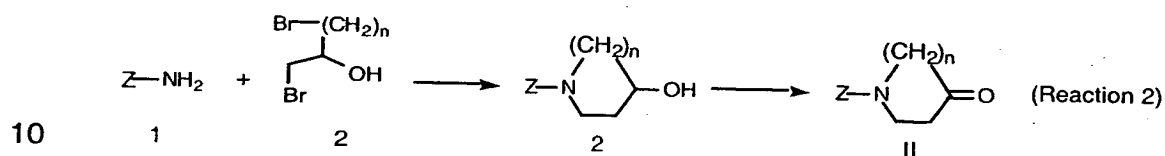
- The compounds of formula I can also be prepared by the coupling (Reaction 1a) of N-protected ketone intermediate IIa with amine intermediate III to give intermediate IV under reductive alkylation conditions such as, titanium isopropoxide/ NaBH_4 , sodium cyanoborohydride, sodium triacetoxyborohydride and the like. Suitable protecting groups include t-butyloxycarbonyl, benzyloxycarbonyl, acetyl, formyl, and the like. The N-protecting group is then cleaved to give intermediate V using standard acidic, basic, or reductive conditions known to those skilled in the art. Intermediate V is then coupled with an appropriate heteroaryl halide using an appropriate base, such as sodium or potassium carbonate, ethanol, methanol, or the like, in solvents, such as acetonitrile, acetone, THF, or the like to give compounds of formula I. Intermediate V can also be condensed with phenyl bromides and other aryl bromides by the Buchwald reaction [Wolfe and Buchwald, *Tetrahedron Letters*, 38 (36), 6359 (1997)] to give compounds of formula I. Other methods known to those skilled in the art can also be used.

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Intermediate Preparation: Formula II Compounds

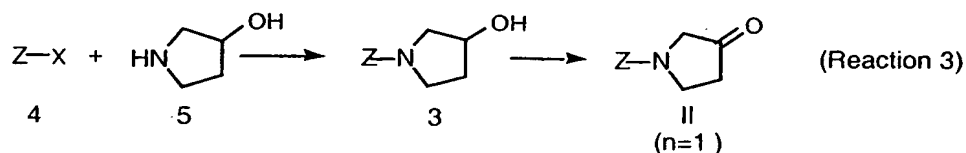
Intermediate ketone compounds of formula II can be prepared by alkylation of an amine (1) with a dihaloalkanol (2) using an appropriate acid scavenger such as an alkali carbonate, e.g. K_2CO_3 in an appropriate organic solvent such as acetonitrile, acetone, THF, ethanol, methanol, or the like. Subsequent oxidation of (2) with an oxidizing agent such as DMSO/oxalyl chloride, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), or the like provides the formula II intermediate.



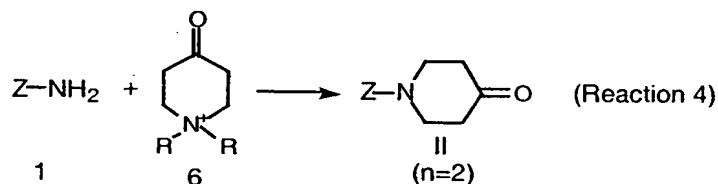
Methods other than Reaction 2 would be known to those skilled in the art for preparation of compounds of formula II. Some examples follow.

Alternatively, pyrrolidin-3-one intermediates of Formula II ($n=1$) can be prepared by coupling of a heteroaryl halide (4) with 3-pyrrolidinol (5) in Reaction 3. Such couplings can be done using an appropriate base, such as sodium or potassium carbonate, ethanol, methanol, or the like, in solvents, such as acetonitrile, acetone, THF, or the like. Subsequent oxidation of the intermediate pyrrolidinol (3) then provides the pyrrolidin-3-one of formula II. Such oxidations can be done using oxidizing agents, such as PCC, PDC, DMSO/oxalyl chloride, or the like. Other methods known to those skilled in the art may also be used.

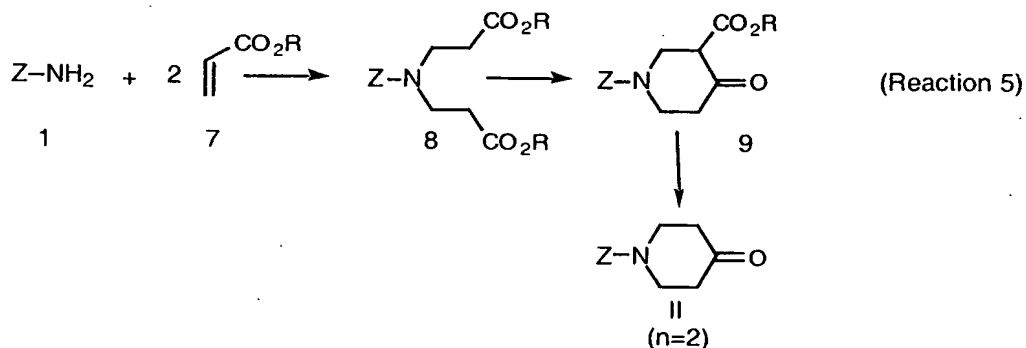
-9-



- 4-Piperidone intermediates of formula II ($n=2$) are most conveniently prepared in Reaction 4 of an aniline or heterocyclic amine (1) with quaternary alkyl ammonium salts of 4-piperidone (6; R=alkyl). Such reactions can be carried out using an appropriate base, such as sodium or potassium carbonate, or the like, in solvents, such as acetonitrile, acetone, THF, ethanol, methanol, or the like. Other methods known to those skilled in the art may also be used.

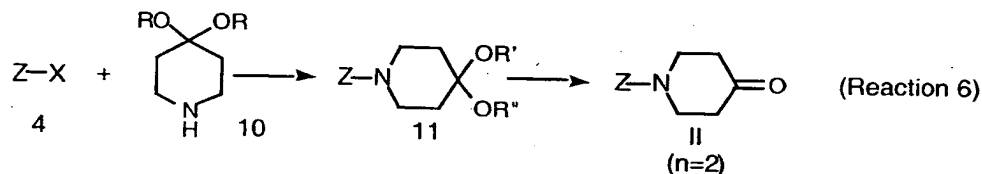


- As shown in Reaction 5, 4-piperidone intermediates of formula II ($n=2$) can be prepared by the reaction of an aniline or heterocyclic amine (1) with esters of acrylic acid (7). The diester intermediate (8) is then reacted with a base, such as sodium or potassium alkoxides, sodium hydride, or the like, in solvents such as THF, diethyl ether, benzene, toluene, or the like, to give the keto-ester intermediate (9). Subsequent hydrolysis and decarboxylation of the keto-ester intermediate, under basic or acidic conditions known to those skilled in the art, gives the 4-piperidone intermediates of formula II ($n=2$). Other methods known to those skilled in the art may also be used.

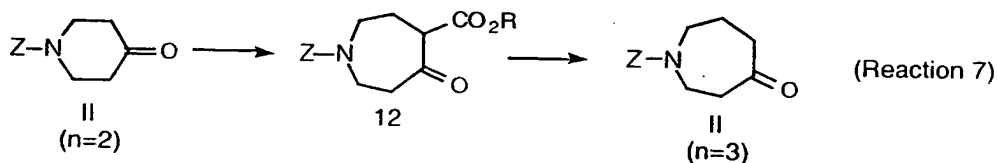


-10-

Alternatively, in Reaction 6 4-piperidone intermediates of formula II (n=2) can be prepared by coupling of a heteroaryl halide (4) with ketals of 4-piperidone (10; R=alkyl). Such couplings can be done using an appropriate base, such as sodium or potassium carbonate, ethanol, methanol, or the like, in solvents, such as acetonitrile, acetone, THF, or the like. Intermediate 10 can also be condensed with phenyl bromides and other aryl bromides by the Buchwald reaction [Wolfe and Buchwald, Tetrahedron Letters, 38 (36), 6359 (1997)] to give the 1-aryl intermediate (11). Subsequent cleavage of the intermediate 1-aryl ketal intermediate (11), then provides the 4-piperidone intermediates of formula II (n=2). Suitable acidic conditions for such cleavages include: dilute aqueous HCl, acetone/HCl, THF/HCl, acetone/H₂SO₄, THF/ H₂SO₄, dioxane/HCl, and the like. Acids suitable for this ketal hydrolysis include, but are not limited to, hydrochloric, sulfuric, acetic, phosphoric, paratoluene-sulfonic, methanesulfonic, benzoic and the like. Other methods known to those skilled in the art may also be used.



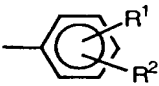
Azepin-4-one intermediates of formula II (n=3) are conveniently prepared by ring expansion (Reaction 7) of the corresponding 1-aryl-4-piperidone. Such ring expansions can be done using esters of diazoacetic acid, with Lewis acid catalysts such as BF₃•Et₂O or the like, in solvents, such as diethyl ether, THF, or the like. Subsequent hydrolysis and decarboxylation of the keto-ester intermediate, under basic or acidic conditions known to those skilled in the art, then provides the azepin-4-one intermediates of formula II (n=3). Other methods known to those skilled in the art may also be used.



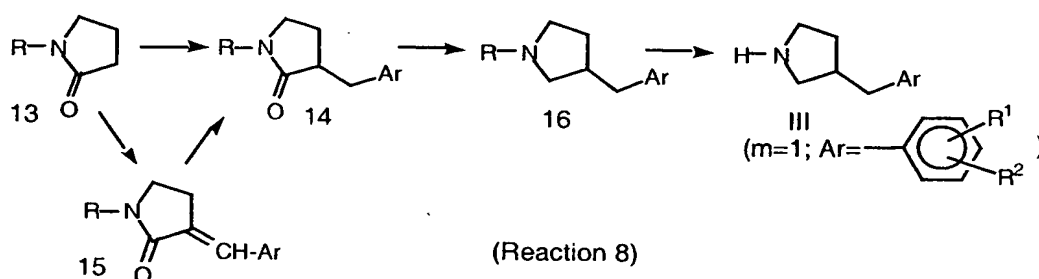
-11-

Intermediate Preparation: Formula III Compounds

The pyrrolidine intermediates of formula III ($m=1$) are conveniently prepared by monoalkylation of a 1-protected-pyrrolidin-2-one (13: R is alkyl, benzyl, etc.) with alkylating agents such as benzyl halides, tosylates, mesylates, or the like, using bases such as LDA, LiTMP, or the like, in solvents such as THF, diethyl ether, hexane, or the like, to give the benzyl pyrrolidinone intermediate (14). Suitable protecting groups include trimethylsilyl, methyl, benzyl, and the like. Alternatively, the 1-protected-pyrrolidin-2-one (13) can be condensed with a substituted benzaldehyde using bases such as NaH, LDA, LiTMP, sodium or potassium alkoxides, or the like, in solvents such as THF, diethyl ether, benzene, toluene, or the like. Subsequent reduction of the benzylidene intermediate (15: Ar is



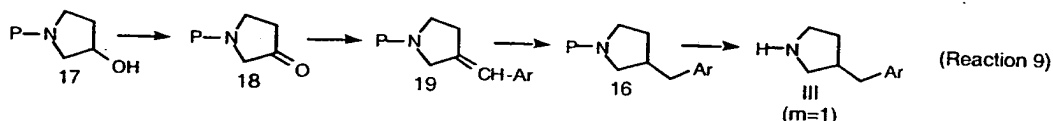
in solvents such as ethanol, ethyl acetate, or the like, provides the benzyl pyrrolidinone intermediate (14). Reduction of the benzyl pyrrolidinone intermediate (14) with reducing agents such as LAH, borane, or the like, provides the 1-protected-pyrrolidine intermediate (16). Subsequent cleavage of the N-protecting group using methods known to those skilled in the art provides the pyrrolidine intermediates of formula III ($m=1$) as shown in Reaction 8.



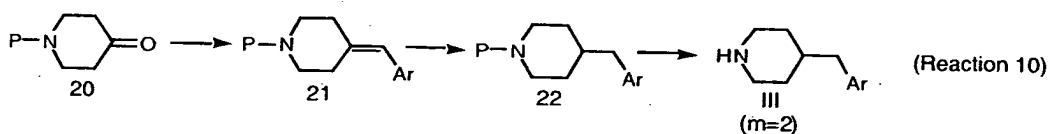
Alternatively, as shown in Reaction 9 an N-protected pyrrolidin-3-ol (17: P is an N-protecting group) can be oxidized to the pyrrolidin-3-one (18). Condensation of ketone (18) with reagents such as benzyl phosphonate esters using bases such as NaH, LDA, sodium or potassium alkoxides, or the like, in solvents such as THF, diethyl ether, or the like, provides the benzylidene intermediate (19). Subsequent reduction of the benzylidene

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group using hydrogen and platinum, palladium, or ruthenium catalysts, in solvents such as ethanol, ethyl acetate, or the like, provides the N-protected pyrrolidine intermediate (16). The N-protecting group is then cleaved using methods known to those skilled in the art to give the pyrrolidine intermediates of formula III (m=1) as depicted in Reaction 9.



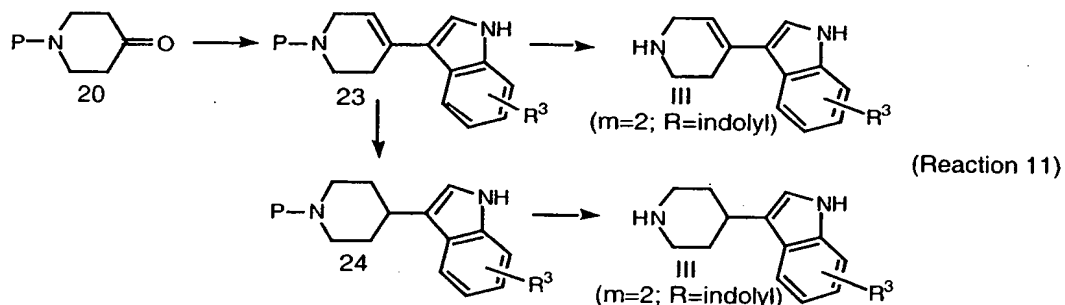
The piperidine intermediates of formula III (m=2) are conveniently prepared by condensation of an N-protected-4-piperidone (20) with reagents such as benzyl phosphonate esters using bases such as NaH, LDA, sodium or potassium alkoxides, or the like, in solvents such as THF, diethyl ether, or the like, provides the benzylidene intermediate (21). Subsequent reduction of the benzylidene group using hydrogen and platinum, palladium, or ruthenium catalysts, in solvents such as ethanol, ethyl acetate, or the like, provides the piperidine intermediate (22). The N-protecting group is then cleaved using methods known to those skilled in the art to give the piperidine intermediates of formula III (m=2) as depicted in Reaction 10.



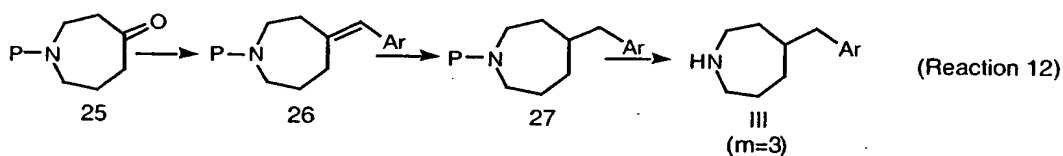
The piperidine intermediates of formula III (m=1; Y= 3-indolyl) can be prepared by condensing an N-protected-4-piperidone (20) with a substituted indole using catalysts such as pyrrolidine, acetic acid, or the like, in solvents such as ethanol, benzene, THF, or the like, to give the tetrahydropyridine intermediates (23). Cleavage of the N-protecting group provides the tetrahydropyridines of formula III (m=1; Y= 3-indolyl). Alternatively, as shown in Reaction 11 the tetrahydropyridine intermediates (23) can be reduced using hydrogen and a suitable catalyst such as platinum, palladium, or ruthenium catalysts, in solvents such as ethanol, ethyl acetate, or the like, to give the piperidine intermediates (24). The N-protecting group is then

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cleaved using methods known to those skilled in the art to give the piperidine intermediates of formula III ($m=1$; $Y=3$ -indolyl).



The 4-substituted azepine intermediates of formula III ($m=3$) are conveniently prepared by condensation of an N-protected-4-azepinone (25) with reagents such as benzyl phosphonate esters using bases such as NaH, LDA, sodium or potassium alkoxides, or the like, in solvents such as THF, diethyl ether, or the like, provides the benzylidene intermediate (26). Subsequent reduction of the benzylidene group using hydrogen and platinum, palladium, or ruthenium catalysts, in solvents such as ethanol, ethyl acetate, or the like, provides the benzyl azepine intermediate (27). The N-protecting group is then cleaved using methods known to those skilled in the art to give the azepine intermediates of formula III ($m=3$) as shown in Reaction 12.



15

The reactions depicted above and their application are familiar to the practitioner skilled in organic synthesis and modifications of conditions and reagents would be readily understood. The skilled synthetic chemist would know how to adapt these processes for preparation of specific formula I compound including other compounds embraced by this invention but not specifically disclosed. Variations of the methods to produce the same compounds in somewhat different fashion will also be evident to one skilled

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in the art. To provide greater detail in description, representative synthetic examples are provided infra in the "Specific Embodiments" section.

5 The compounds of formula I show potent inhibition of 5-HT re-uptake and can be envisioned as potential agents for disorders associated with dysfunction in serotonergic neurotransmission. Such disorders may include depression, anxiety, eating disorders, obesity, and drug abuse. In particular, the active compounds of the instant series are envisioned as specific agents for treating depression.

10 The compounds comprising the present invention inhibit the re-uptake of endogenous serotonin. Selective inhibitors of serotonin uptake are effective for the treatment of mental depression and have been reported to be useful for treating chronic pain (see: R.W. Fuller, Pharmacologic Modification of Serotonergic Function: Drugs for the Study and Treatment of Psychiatric and Other Disorders," J. Clin. Psychiatry, 47:4 (Suppl.) April 15 1986, pp. 4-8). Compounds of the present invention are also envisioned to be useful in the following disorders: obsessive-compulsive disorder, feeding disorders, anxiety disorders and panic disorders.

Determination of endogenous monoaminergic re-uptake inhibition values both for serotonin and norepinephrine was accomplished using test 20 methods described by P. Skolnick, et al., Br. J. Pharmacology, (1985), 86, pp. 637-644; with only minor modifications. In vitro IC_{50} (nM) test values were determined for representative compounds of Formula I based on their inhibition of synaptosomal re-uptake of tritiated serotonin. Test data IC_{50} values lower than 500 nM are considered to reflect activity as an inhibitor of 25 serotonin re-uptake. Compounds with IC_{50} values lower than 100 nM comprise preferred compounds and those with IC_{50} value less than 10 nM are most preferred.

Another aspect of the instant invention provides a method for treating 30 a mammal afflicted with depression or chronic pain which comprises administering systemically to said mammal a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable acid addition salt thereof.

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The administration and dosage regimen of compounds of formula I are considered to be done in the same manner as for the reference compound fluoxetine, cf: Schatzberg, et al., J. Clin. Psychopharmacology 7/6 Suppl. (1987) pp. 4451-4495, and references therein. Although the dosage and dosage regimen must in each case be carefully adjusted, utilizing sound professional judgement and considering the age, weight and condition of the recipient, the route of administration and the nature and gravity of the illness, generally the daily dose will be from about 0.05 to about 10 mg/kg, preferably 0.1 to 2 mg/kg, when administered parenterally and from about 1 to about 50 mg/kg, preferably about 5 to 20 mg/kg, when administered orally. In some instances, a sufficient therapeutic effect can be obtained at lower doses while in others, larger doses will be required. Systemic administration refers to oral, rectal and parenteral (i.e. intramuscular, intravenous and subcutaneous). Generally, it will be found that when a compound of the present invention is administered orally, a larger quantity of the active agent is required to produce the same effect as a similar quantity given parenterally. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level that will produce effective antidepressant effects without causing any harmful or untoward side effects.

The compounds of the present invention may be administered for antidepressant purposes either as individual therapeutic agents or as mixtures with other therapeutic agents. Therapeutically, they are generally given as pharmaceutical compositions comprised of an antidepressant amount of a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions which provide from about 1 to 500 mg of the active ingredient per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspensions, syrups, elixirs, and aqueous solutions.

The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration. For example, oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g. starch) and wetting

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agents (e.g. sodium lauryl sulfate). Solutions or suspensions of a formula I compound with conventional pharmaceutical vehicles are employed for parenteral compositions such as an aqueous solution for intravenous injection or an oily suspension for intramuscular injection.

5

Description of Specific Embodiments

The compounds which constitute this invention, their methods of preparation and their biologic actions will appear more fully from consideration of the following examples, which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees Celsius and melting points are uncorrected. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts in the ^1H NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), heptet (hept), quartet (q), triplet (t) or doublet (d). Abbreviations employed are DMSO- d_6 (deuterodimethylsulfoxide), CDCl_3 (deuteriochloroform) and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers (cm^{-1}).

Analytical thin-layer chromatography (TLC) was performed on 0.25 mm EM silica gel 60 F-254 coated glass plates and preparative flash chromatography was performed on EM silica gel (36-62 μm). The solvent systems used are reported where appropriate. All reaction, extraction and chromatography solvents were reagent grade and used without further purification except tetrahydrofuran (THF) which was distilled from sodium/benzophenone ketyl. All non-aqueous reactions were carried out in flame-dried glassware under a nitrogen atmosphere.

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A. Synthesis of Intermediates

Compounds of Formula IIExample 11-(3-Cyanophenyl)-3-pyrrolidinone

- 5 A mixture of 3-aminobenzonitrile (3.0 g, 25.4 mmol) 1,4dibromobutan-2-ol (8.8 g, 4.4 ml, 38.1 mmole), potassium carbonate (7.7 g, 55.7 mmole), and triethyl phosphite (20 ml) was heated to 130 °C for 18 hr. The mixture was cooled, diluted with water, and extracted twice with ethyl ether. The ether extracts were dried over magnesium sulfate and concentrated in vacuo.
- 10 The residue was purified by chromatography on silica gel using ethyl acetate/hexane (25% to 67% gradient) as the eluent to give 1-(3-cyanophenyl)-3-pyrrolidinol (7.4 g, 50%).

- A solution of 1-(3-cyanophenyl)-3-pyrrolidinol (0.65 g, 4.1 mmol) in triethyl amine (5.72 ml, 41 mmol) and DMSO (15 ml) was cooled to 0 °C and
- 15 pyridine-SO₃ (1.96 g, 12.3 mmol) was added. The mixture was stirred at 0 °C for 1 hr and at room temperature for 18 hr. The reaction mixture was poured into water (100 ml) and extracted three times with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and concentrated in vacuo to give 1-(3-cyanophenyl)-3-pyrrolidinone (0.41 g,
- 20 54%) that was used without purification.

Also prepared by this general method were:

1-(2,6-dimethoxyphenyl)-3-pyrrolidinone.

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Example 21-(Benzodioxol-5-yl)-4-piperidone

A slurry of 1-benzyl-4-piperidone methiodide (5.43 g, 16.4 mmol) in water (10 ml) was added over 30 min to a gently refluxing mixture of 5-amino-benzodioxole (1.86 g, 13.6 mmol) and potassium carbonate (0.2 g, 1.4 mmol) in ethanol (25 ml). Water (25 ml) was added portion wise over 30 min, and the mixture was heated to reflux for an additional 30 min. The mixture was cooled and the ethanol removed *in vacuo*. Water (25 ml) was added and the mixture was extracted twice with methylene chloride (25 ml). The organic extracts were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using CHCl₃ as the eluent to give the 1-(Benzodioxol-5-yl)-4-piperidone (2.0 g, 67%). MS (esi): 220 (M+H)⁺. ¹H-NMR (300 MHz, CDCl₃): δ 2.56 (t, 4H), 3.44 (t, 4H), 5.92 (s, 2H), 6.44 (dd, 1H), 6.60 (d, 1H), 6.74 (d, 1H).

Also prepared by this general method were:

1-(2-methoxyphenyl)-4-piperidone, 32% yield;

1-(2,3-dimethoxyphenyl)-4-piperidone;

1-(3,4-dimethoxyphenyl)-4-piperidone, 55% yield;

1-(2,4-dimethoxyphenyl)-4-piperidone;

1-(2,5-dimethoxyphenyl)-4-piperidone, 44% yield;

1-(2,6-dimethoxyphenyl)-4-piperidone, 18% yield;

1-(3-cyanophenyl)-4-piperidone, 28% yield;

1-(3-chloro-4-cyanophenyl)-4-piperidone, 48% yield;

1-(3-fluoro-4-methoxyphenyl)-4-piperidone, 28% yield;

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- 1-(3-fluoro-2-methoxyphenyl)-4-piperidone;
- 1-(benzothiazol-5-yl)-4-piperidone;
- 1-(2-methylbenzothiazol-5-yl)-4-piperidone, 100% yield;
- 1-(quinolin-4-yl)-4-piperidone;
- 5 1-(quinolin-5-yl)-4-piperidone;
- 1-(2,3-dihydro-1,4-benzodioxan-6-yl)-4-piperidone, 99% yield;
- 1-(4,5-dimethoxy-2-methylphenyl)-4-piperidone;
- 1-(1,3,5-trimethoxyphenyl)-4-piperidone;
- 1-(2-methoxypyridin-5-yl)-4-piperidone;
- 10 1-(2,4,5-trimethoxyphenyl)-4-piperidone;
- 1-(7-methoxy-2H,3H,4H-benzo[b]1,5-dioxepin-8-yl)-4-piperidone.

Example 3

1-(6-chloropyrimidin-4-yl)-4-piperidone

- 15 A mixture of 4-piperidone ethylene ketal (7.15 g, 50 mmol), 4,6-dichloropyrimidine (7.45 g, 50 mmol), and potassium carbonate (10 g) in acetonitrile (75 ml) was stirred for 18 hr and then heated to reflux for 1 hr. The mixture was cooled and filtered. The filtrate was concentrated *in vacuo* to give a white solid. The crude 1-(6-chloropyrimidin-4-yl)-4-piperidone
- 20 ethylene ketal was recrystallized from c-hexane to give white powder (11.7 g, 92 %, mp: 112-114 °C).

A solution of 1-(6-chloropyrimidin-4-yl)-4-piperidone ethylene ketal (2 g, 7.83 mmol) in acetone (25 ml) and 1N HCl (25 ml) was stirred for 18 hr.

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The acetone was removed *in vacuo* and the mixture made basic with saturated sodium carbonate. The mixture was extracted twice with ethyl acetate. The extracts were combined, dried with brine, and concentrated *in vacuo* to give 1-(6-chloropyrimidin-4-yl)-4-piperidone as a white powder (1.6 g, 96.6 %, mp: 100-103 °C).

Also prepared by this general method were:

1-(2-chloropyrimidin-4-yl)-4-piperidone;

1-(6-chloropyrazin-2-yl)-4-piperidone;

1-(6-chloropyridazin-3-yl)-4-piperidone;

10 1-(5-cyanopyridin-2-yl)-4-piperidone;

1-(4-cyanophenyl)-4-piperidone, 48%;

1-(3-chloro-4-cyanophenyl)-4-piperidone, 48%;

Example 4

15 1-(6-methoxypyrimidin-4-yl)-4-piperidone

A solution of 1-(6-chloropyrimidin-4-yl)-4-piperidone ethylene ketal (2g, 8.87 mmol), sodium methoxide (prepared from 0.8 g sodium metal, 34.8 mmol), in methanol (50 ml) was heated to reflux for 17 hr. The mixture was cooled and concentrated *in vacuo*. The crude 1-(6-methoxypyrimidin-4-yl)-4-piperidone ethylene ketal was washed with water, filtered, and air dried (1.42 g, 63.8 %, 81-82.5 °C).

A solution of 1-(6-methoxypyrimidin-4-yl)-4-piperidone ethylene ketal (1.38 g, 5.5 mmol) in acetone (25 ml) and 1N HCl (25 ml) was stirred for 18 hr. The acetone was removed *in vacuo* and the mixture made basic with saturated sodium carbonate. The mixture was extracted twice with ethyl

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acetate. The extracts were combined, dried with brine, and concentrated *in vacuo* to give 1-(6-methoxypyrimidin-4-yl)-4-piperidone as a white powder (0.95 g, 83.5 %, mp: 111-114 °C).

Also prepared by this general method were:

5 1-(2-methoxypyrimidin-4-yl)-4-piperidone;

1-(6-methoxypyrazin-2-yl)-4-piperidone;

1-(6-methoxypyridazin-3-yl)-4-piperidone.

Example 5

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1-(pyrimidin-4-yl)-4-piperidone

15 A solution of 1-(6-chloropyrimidin-4-yl)-4-piperidone ethylene ketal (2g, 8.87 mmol) in ethanol (25 ml) and ethyl acetate (25 ml) was hydrogenated at 60 psi for 1 hr over 10% Pd/C (0.25 g). The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in methylene chloride and filtered through celite. The filtrate was concentrated *in vacuo* to give 1-(pyrimidin-4-yl)-4-piperidone ethylene as a white solid (112-115 °C).

20 The 1-(pyrimidin-4-yl)-4-piperidone ethylene ketal was dissolved in acetone (25 ml) and 1N HCl (25 ml) was stirred for 18 hr. The acetone was removed *in vacuo* and the mixture made basic with saturated sodium carbonate. The mixture was extracted twice with ethyl acetate. The extracts were combined, dried with brine, and concentrated *in vacuo* to give 1-(pyrimidin-4-yl)-4-piperidone as a white powder (0.80 g, 51.4 % for two steps, mp: 61-65 °C).

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Also prepared by this general method were:

1-(pyrazin-2-yl)-4-piperidone;

1-(pyridazin-3-yl)-4-piperidone.

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Example 5A

1-(5-cyano-2-methoxyphenyl)-4-piperidone

1,4-Dioxo-8-azaspiro[4.5]decane (1.47 g, 10.28 mmol), sodium bis(trimethylsilyl)amide (1N in THF, 12 ml), and $\text{PdCl}_2(\text{p}(\text{o-tolyl})_3)_2$ [2 mol % catalyst prepared from bis(acetonitrile) Pd(II) chloride (53 mg, 0.206 mmol) and tri(o-tolyl)phosphine (125 mg, 0.52 mmol)] were added to a solution of 3-bromo-4-methoxybenzonitrile (1.82 g, 8.58 mmol) in toluene (40 ml). The reaction was stirred for 5 hours at 100 °C. The reaction was concentrated *in vacuo*, diluted with water, and extracted with methylene chloride. The organic extract was concentrated *in vacuo*, and the residue purified by chromatography on silica gel using hexane/ethyl acetate (80/20) as the eluent to give 1-(5-cyano-2-methoxyphenyl)-4-piperidone ethylene ketal (900 mg, 38%). This ketal was dissolved in dioxane (15 ml) and HCl (6 N, 2.2 ml) and stirred at 100 °C for 2h. The solution was cooled, quenched with saturated aqueous NaHCO_3 . The mixture was extracted with methylene chloride, concentrated *in vacuo*, and purified by chromatography on silica gel using hexane/ethyl acetate (80/20) as the eluent to give 1-(5-cyano-2-methoxyphenyl)-4-piperidone (125 mg, 19 %).

Compounds of Formula III

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Example 6

3-(2-bromobenzyl)pyrrolidine

1-(Trimethylsilyl)-2-pyrrolidinone (7.39 g, 51.7 mmol) was added slowly to a solution of lithium diisopropylamide (25 ml, 2M in heptane/THF/ethylbenzene, 50 mmol) and THF (10 ml) at -78°C. The solution was stirred

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for 1 hr, and 2-bromobenzyl bromide (6 ml, 46.5 mmol) was added dropwise. The solution was stirred for 2 hr and quenched with 1N HCl. The organic layer was separated, washed with water, and concentrated *in vacuo*. The residue was dissolved in methanol, and heated to reflux with HCl (5 ml of 37%) and tetrabutylammonium fluoride (10 ml of 1M in THF, 10 mmol), for 15 min. The solution was made basic with saturated Na_2CO_3 and concentrated *in vacuo*. The residue was dissolved in CHCl_3 , washed with water, and concentrated *in vacuo* to give an oil. This crude product was purified by chromatography on silica gel using 5% methanol/ CH_2Cl_2 as the eluent to give 3-(2-bromobenzyl)pyrrolidin-3-one as an oil (9.5 g, 80.4%).

A solution of 3-(2-bromobenzyl)pyrrolidin-3-one (5.0 g, 19.7 mmol) in THF (10 ml) was added slowly to a solution of AlH_3 (freshly prepared from 1M LAH in THF (50 ml) and 98% H_2SO_4 (1.3 ml) at 0°C). The mixture was stirred for 4 hr, cooled to 0°C , and slowly quenched with water and 10N NaOH. The mixture was diluted with ether and filtered. The filtrate was washed with brine and concentrated *in vacuo* to an oil. The oil was purified by short path vacuum distillation to give 3-(2-bromobenzyl)pyrrolidine as an oil (3.2 g, 67.7%).

Also prepared by this general method was:

3-(2,5-difluorobenzyl)pyrrolidine.

Example 7

4-(2-bromobenzyl)piperidine

A solution of dimethyl 2-bromobenzylphosphonate (45.66 g, 148.9 mmol) in THF was added slowly to a mixture of NaH (7.14 g of a 60% mineral oil dispersion, 178.5 mmol) in THF (200 ml) and the mixture was stirred for 1 hr. A solution of 1-(tert-butoxycarbonyl)-4-piperidinone (29.67 g, 148.9 mmol) in THF was added dropwise and the mixture was heated to reflux for 1.5 hr. The mixture was cooled and quenched with brine. The mixture was diluted with ethyl acetate, washed with water, and dried with brine. The organic layer was concentrated *in vacuo* to an oil. The oil was dissolved in

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acetonitrile and extracted with hexane. The acetonitrile layer was concentrated *in vacuo* to give 1-(tert-butoxycarbonyl)-4-[(2-bromophenyl)methylene]piperidine as an oil that solidified upon standing (48.3 g, 97%).

- 5 A solution of 1-(tert-butoxycarbonyl)-4-[(2-bromophenyl)methylene]-piperidine (8 g, 22.7 mmole) in ethyl acetate (75 ml) and ethanol (75 ml) was shaken with PtO₂ (0.75 g) and hydrogen (60 psi) for 15 min. Two further batches of 1-(tert-butoxycarbonyl)-4-[(2-bromophenyl)-methylene]-piperidine (8 g each, 24 g total) were similarly reduced and the mixtures were filtered.
- 10 The filtrates were combined and concentrated *in vacuo*. The residue was dissolved in dioxane (200 ml) and 3N HCl (100 ml) and stirred for 18 hr. The solution was concentrated *in vacuo* and the residue was made basic with 50% sodium hydroxide. The mixture was extracted with CH₂Cl₂. The extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give a yellow
- 15 oil that was purified by short path vacuum distillation to give 4-(2-bromobenzyl)piperidine as a oil (15 g, 86.6%). The oil converted to the fumarate salt using fumaric acid (6.85 g) in 2-propanol to give 4-(2-bromobenzyl)piperidine fumarate as a white solid (15.8 g, 62.6% overall, mp: 164-165 °C).
- 20 Also prepared by this general method were:
- 4-(2-bromo-5-fluorobenzyl)piperidine;
- 4-(2-bromo-5-methoxybenzyl)piperidine;
- 4-(2,5-dichlorobenzyl)piperidine;
- 25 4-(2-chlorobenzyl)piperidine.

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Example 8hexahydro-4H-4-(2-bromobenzyl)azepine

Di-tert-butyl dicarbonate (4.1 g, 18.7 mmol) was added to a stirred solution of hexahydro-4H-azepin-4-one (2.8 g, 18.7 mmol) and NaHCO_3 (1.6 g, 18.7 mmol) in water (70 ml) and CH_2Cl_2 (70 ml). The mixture was stirred for 20 hr. The organic layer was separated, dried over Na_2SO_4 , and concentrated *in vacuo* to give 1-(tert-butyloxycarbonyl)-hexahydro-4H-azepin-4-one as an amber oil (3.98 g, 100%).

A solution of dimethyl 2-bromobenzylphosphonate (5.5 g, 18.7 mmol) in THF was added slowly to a mixture of NaH (0.8 g of a 60% mineral oil dispersion, 20 mmol) in THF (75 ml) and ethanol (0.5 ml) and the mixture was stirred for 45 min. A solution of 1-(tert-butyloxycarbonyl)-hexahydro-4H-azepin-4-one (3.98 g, 18.7 mmol) in THF was added dropwise and the mixture was heated to reflux for 5 hr. The mixture was cooled and quenched with water. The mixture was diluted with ethyl acetate, washed with water, and dried with brine. The organic layer was concentrated *in vacuo*. The residue was purified by chromatography on silica gel using 5% ethyl acetate/hexane to give 1-(tert-butoxycarbonyl)-4-[(2-bromophenyl)methylene]-hexahydro-4H-azepine as a clear oil that solidified upon standing (4.3 g, 62.8%).

A solution of 1-(tert-butoxycarbonyl)-4-[(2-bromophenyl)methylene]-hexahydro-4H-azepine (4.3 g, 11.7 mmol) in ethyl acetate (50 ml) and ethanol (30 ml) was shaken with PtO_2 (0.4 g) and hydrogen (60 psi) for 15 min. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in dioxane (100 ml) and 2N HCl (50 ml). The solution was stirred for 18 hr, and then concentrated *in vacuo*. The residue was made basic with saturated Na_2CO_3 . The mixture was extracted with CH_2Cl_2 . The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was converted to the fumarate salt in 2-propanol to give hexahydro-4H-4-(2-bromobenzyl)azepine fumarate as a white powder (2.5 g, 79.7%, mp: 148-150 °C).

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B. Synthesis of Formula I Products

Example 95-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2H-benzo[d]1,3-dioxolane

- 5 A solution of 1-(benzodioxol-5-yl)-4-piperidone (1.5 g, 6.84 mmol) and
4-(2-bromo-5-fluorobenzyl)piperidine (2.4 g, 8.89 mmol) and sodium
triacetoxy-borohydride (2.5 g, 11.63 mmol) in THF (25 ml) and acetic acid
(0.39 ml) was stirred over 4Å sieves for 18 hr. The mixture was filtered. 1N
NaOH (10 ml) was added to the filtrate, which was then concentrated *in*
10 *vacuo*. The residue was dissolved in CHCl₃ (50 ml) and extracted with water.
The CHCl₃ layer was concentrated *in vacuo* to give an oil (4.2 g) which was
crystallized from isopropyl ether. This crude product was purified by
chromatography on silica gel using 30% acetone/CH₂Cl₂ as the eluent to give
15 5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2H-benzo[d]1,3-
dioxolane (1.2 g, 37%). This material was converted to the dihydrochloride
salt (mp: 272-273 °C).

Also prepared by this general method were:

- 2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-1,3-dimethoxybenzene;
- 3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl} piperidyl)-6-
20 chloropyridazine;
- 5-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) quinoline;
- 3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl)
benzenecarbonitrile;
- 2-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) pyrimidine;
- 25 1-{4-[4-(5-fluoroindol-3-yl)piperidyl]piperidyl}-2,4-dimethoxybenzene;

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- 3-[1-(1-(2H,3H-benzo[3,4-3]1,4-dioxan-6-yl)-4-piperidyl)-4-piperidyl]indole-5-carbonitrile;
- 3-{1-[1-(2,4-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;
- 3-[1-(1-(5-quinolyl)-4-piperidyl)-4-piperidyl]indole-5-carbonitrile;
- 5 3-{1-[1-(2-methylbenzothiazol-5-yl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;
- 3-{1-[1-(2,6-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;
- 1-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;
- 10 1-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;
- 1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;
- 2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-1,3,5-trimethoxybenzene;
- 15 5-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5-(4-{4-[(2-chlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 20 5-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
- 3-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;

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4-methoxy-3-(4-{4-[(3-methoxyphenyl)methyl]piperidyl}piperidyl)benzenecarbonitrile;

3-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;

5 1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2,4,5-trimethoxybenzene;

8-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-7-methoxy-2H,3H,4H-benzo[b]1,5-dioxepin.

10

Example 102-(4-{4-[(2,5-Dichlorophenyl)methyl]piperidinyl}hexahydro-4H-azepine)pyrimidine

A solution of 1-(tert-butyloxycarbonyl)-hexahydro-4H-azepin-4-one (650 mg, 3 mol), 4-(2,5-dichlorobenzyl)piperidine (732 mg, 2.24 mmol),
15 sodium triacetoxyborohydride (825 mg, 3.9 mmol), acetic acid (0.17 ml, 3 mmol), and trimethyl orthoformate (0.640 ml, 6 mmol) in dichloroethane (5 ml) was stirred for 36 hr at room temperature. The reaction was quenched with 1N NaOH and stirred for 2 hr. The mixture was extracted with
20 methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel using ethyl acetate/isopropanol as the eluent to give 1-(tert-butyloxycarbonyl)-4-[[[(2,5-dichlorophenyl)methyl]piperid-1-yl]hexahydro-4H-azepine (889 mg, 67%).

A solution of 1-(tert-butyloxycarbonyl)-4-[[[(2,5-
25 dichlorophenyl)methyl]piperid-1-yl]hexahydro-4H-azepine (700 mg, 1.58 mmol) in trifluoroacetic acid (2 ml) and methylene chloride (0.5 ml) was stirred at room temperature for 15 min. The solution was concentrated *in vacuo* and the residue was dissolved in chloroform and extracted with saturated aqueous sodium carbonate. The chloroform extract was dried over

-29-

sodium sulfate and concentrated in vacuo to give 4-[(2,5-dichlorophenyl)methyl]piperid-1-yl}hexahydro-4H-azepine (489 mg, 90%).

5 A mixture of 4-[(2,5-dichlorophenyl)methyl]piperid-1-yl}hexahydro-4H-azepine (236 mg, 0.69 mmol), 2-chloropyridine (237 mg, 2.07 mmol), and potassium carbonate (190 mg, 1.38 mmol) in dimethyl formamide (5 ml) was heated to 70 °C for 20 or. The mixture was diluted with water and extracted three times with ethyl acetate. The combined ethyl acetate extracts were extracted with water five times and dried with brine and sodium sulfate. The extracts were concentrated in vacuo and the residue purified by
10 chromatography on silica gel using methylene chloride/methanol as the eluent to give 2-(4-{4-[(2,5-dichlorophenyl)methyl]piperidinyl}hexahydro-4H-azepine)pyrimidine (198 mg, 69%).

Also prepared by this general method were:

15 2-(4-{4-[(2-bromophenyl)methyl]piperidinyl}hexahydro-4H-azepine)pyrimidine, 47%;

2-(4-{4-[(2,5-dichlorophenyl)methyl]piperidinyl}hexahydro-4H-azepine)-3-chloropyridazine, 65%;

20 2-(4-{4-[(2-bromophenyl)methyl]piperidinyl}hexahydro-4H-azepine)-3-chloropyridazine, 29%.

Example 11

Serotonin Transporter Binding Assay

Tissue Preparation. HEK-293 cells that stably express human serotonin transporters (HEK-hSERT cells) were grown at 37 °C in 5% CO₂ as
25 a monolayer in medium consisting of EMEM supplemented with 10% fetal bovine serum and G418 sulfate (500 µg/ml). To prepare membranes for radioligand binding experiments, cells were rinsed twice with phosphate-buffered saline (138 mM NaCl, 4.1 mM KCl, 5.1 mM Na₂PO₄, 1.5 mM KH₂PO₄, 11.1 mM glucose, pH 7.4). Cells were transferred from plates to

-30-

polypropylene tubes (16 x 100 mm), centrifuged at 1,200 x g for 5 min and were frozen at -80 °C until assay. Following centrifugation, pellets were resuspended by homogenization in buffer consisting of 50 mM Tris (pH 7.7 at 25 °C), 120 mM NaCl and 5 mM KCl and then centrifuged at 32,000 x g for 10 min. Following centrifugation, supernatants were discarded and pellets were resuspended in buffer consisting of 50 mM Tris (pH 7.4 at 25 °C), 150 mM NaCl and 5 mM KCl.

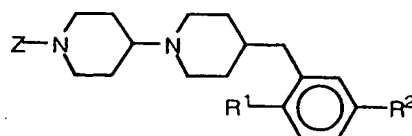
High-affinity binding assay. Membrane homogenates (200 μ l/plate) were incubated with 1 nM [3 H]-citalopram (specific activity = 85 Ci/mmol) and increasing concentrations of test compounds for 1 hour at 25 °C in a total volume of 250 μ l. The assay buffer consisted of 50 mM Tris (pH 7.4 at 25 °C), 120 mM NaCl and 5 mM KCl (pH 7.4 with conc. HCl). Plates were incubated for 1 hour at 25 °C, then filtered through 0.5% PEI treated Whatman GF/B filters using a Brandel cell harvester. Filters were washed three times with 3 ml of ice-cold tris wash buffer. Non-specific binding was defined with 10 μ M fluoxetine.

Data analysis. Amount of radioligand bound in the presence and absence of competitor was analyzed by plotting (-)log drug concentration versus the amount of radioligand specifically bound. The midpoint of the displacement curve (IC_{50} , nM), signifies the potency. K_i values were calculated using the method of Cheng and Prusoff (1973).

Substances which inhibit the re-uptake of serotonin are recognized to be effective antidepressants (Selective Serotonin Reuptake Inhibitors. Edited by JP Feighner and WF Boyer, Chichester, England. John Wiley & Sons, 1991, pp 89-108). The following compounds inhibit the re-uptake of serotonin with K_i < 100 nM:

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Table 1



Example #	Z	R ¹	R ²	Yield %
12	benzodioxan-6-yl	I	methoxy	33
13	3,4-dimethoxyphenyl	Cl	Cl	41
14	3-fluoro-4-methoxyphenyl	Cl	Cl	47
15	benzodioxol-5-yl	Cl	Cl	26
16	benzodioxan-6-yl	Cl	Cl	22
17	3,4-dimethoxyphenyl	F	F	62
18	3-fluoro-4-methoxyphenyl	F	F	61
19	benzodioxol-5-yl	F	F	66
20	benzodioxan-6-yl	F	F	70
21	3,4-dimethoxyphenyl	Br	H	47
22	3-fluoro-4-methoxyphenyl	Br	H	47
23	benzodioxol-5-yl	Br	H	48
24	benzodioxan-6-yl	Br	H	50
25	2-methoxyphenyl	F	F	43
26	2,5-dimethoxyphenyl	F	F	52
27	quinolin-6-yl	F	F	74
28	quinolin-5-yl	F	F	61
29	2-methoxyphenyl	Br	H	32
30	2,5-dimethoxyphenyl	Br	H	40

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Example #	Z	R ¹	R ²	Yield %
31	quinolin-6-yl	Br	H	29
32	quinolin-5-yl	Br	H	8
33	2-methoxyphenyl	Cl	H	58
34	2,5-dimethoxyphenyl	Cl	H	34
35	2,4-dimethoxyphenyl	Cl	H	59
36	quinolin-6-yl	Cl	H	66
37	quinolin-5-yl	Cl	H	43
38	3-fluoro-4-methoxyphenyl	Cl	H	30
39	benzodioxol-5-yl	Cl	H	30
40	benzodioxan-6-yl	Cl	H	42
41	2,5-dimethoxyphenyl	H	methoxy	3
42	3,4-dimethoxyphenyl	H	methoxy	7
43	3-fluoro-4-methoxyphenyl	H	methoxy	7
44	2-methoxyphenyl	Br	F	25
45	2,5-dimethoxyphenyl	Br	F	37
46	quinolin-6-yl	Br	F	33
47	3-fluoro-4-methoxyphenyl	Br	F	21
48	benzodioxol-5-yl	Br	F	34
49	benzodioxan-6-yl	Br	F	24
50	2,5-dimethoxyphenyl	F	methoxy	30
51	quinolin-6-yl	F	methoxy	26
52	3,4-dimethoxyphenyl	F	methoxy	14
53	3-fluoro-4-methoxyphenyl	F	methoxy	11
54	2-methoxyphenyl	Br	methoxy	31

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Example #	Z	R ¹	R ²	Yield %
55	2,5-dimethoxyphenyl	Br	methoxy	25
56	2,4-dimethoxyphenyl	Br	methoxy	27
57	quinolin-6-yl	Br	methoxy	21
58	quinolin-5-yl	Br	methoxy	18
59	3,4-dimethoxyphenyl	Br	methoxy	17
60	benzodioxol-5-yl	Br	methoxy	17
61	benzodioxan-6-yl	Br	methoxy	21
62	2,3-dimethoxyphenyl	Cl	H	33
63	2,3-dimethoxyphenyl	Br	H	37
64	3-fluoro-2-methoxyphenyl	Br	F	6
65	2-methoxyphenyl	Cl	Cl	28
66	2,5-dimethoxyphenyl	Cl	Cl	59
67	2,4-dimethoxyphenyl	Cl	Cl	35
68	2,3-dimethoxyphenyl	Cl	Cl	23
69	3-chloro-4-fluorophenyl	Cl	H	13
70	3-chloro-4-fluorophenyl	F	F	22
71	3-chloro-4-fluorophenyl	Br	H	20
72	3-chloro-4-fluorophenyl	H	methoxy	5
73	3-chloro-4-fluorophenyl	Br	F	17
74	3-chloro-4-fluorophenyl	F	methoxy	21
75	3-chloro-4-fluorophenyl	Br	methoxy	17
76	3-chloro-4-fluorophenyl	Cl	Cl	24
77	2-methyl-benzothiazol-5-yl	Cl	H	19
78	2-methyl-benzothiazol-5-yl	F	F	69

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Example #	Z	R ¹	R ²	Yield %
79	2-methyl-benzothiazol-5-yl	Br	H	26
80	2-methyl-benzothiazol-5-yl	H	methoxy	11
81	2-methyl-benzothiazol-5-yl	Br	F	5
82	2-methyl-benzothiazol-5-yl	F	methoxy	32
83	2-methyl-benzothiazol-5-yl	Br	methoxy	11
84	2-methyl-benzothiazol-5-yl	Cl	Cl	19
85	benzothiazol-6-yl	Cl	H	26
86	benzothiazol-6-yl	F	F	25
87	benzothiazol-6-yl	Br	H	12
88	benzothiazol-6-yl	Br	F	4
89	benzothiazol-6-yl	F	methoxy	21
90	benzothiazol-5-yl	Br	methoxy	3
91	benzothiazol-5-yl	Cl	Cl	18
92	3-cyanophenyl	Cl	H	17
93	3-cyanophenyl	F	F	10
94	3-cyanophenyl	Br	H	22
95	3-cyanophenyl	H	methoxy	7
96	3-cyanophenyl	Br	F	25
97	3-cyanophenyl	F	methoxy	31
98	3-cyanophenyl	Br	methoxy	12
99	3-cyanophenyl	Cl	Cl	33
100	4-cyanophenyl	Cl	H	12
101	4-cyanophenyl	F	F	27
102	4-cyanophenyl	Br	H	20

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Example #	Z	R ¹	R ²	Yield %
103	4-cyanophenyl	H	methoxy	2
104	4-cyanophenyl	Br	F	15
105	4-cyanophenyl	F	methoxy	12
106	4-cyanophenyl	Cl	Cl	16
107	3-chloro-4-cyanophenyl	Cl	H	14
108	3-chloro-4-cyanophenyl	F	F	24
109	3-chloro-4-cyanophenyl	Br	H	13
110	3-chloro-4-cyanophenyl	H	methoxy	14
111	3-chloro-4-cyanophenyl	Br	F	16
112	3-chloro-4-cyanophenyl	F	methoxy	17
113	3-chloro-4-cyanophenyl	Br	methoxy	23
114	3-chloro-4-cyanophenyl	Cl	Cl	19
115	pyrimidin-2-yl	Cl	H	21
116	pyrimidin-2-yl	F	F	42
117	pyrimidin-2-yl	Br	H	28
118	pyrimidin-2-yl	H	methoxy	3
119	pyrimidin-2-yl	Br	F	41
120	pyrimidin-2-yl	F	methoxy	13
121	pyrimidin-2-yl	Br	methoxy	32
122	pyrimidin-2-yl	Cl	Cl	32
123	2-chloropyrimidin-4-yl	Cl	H	22
124	2-chloropyrimidin-4-yl	F	F	20
125	2-chloropyrimidin-4-yl	Br	H	10
126	2-chloropyrimidin-4-yl	Br	F	23

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Example #	Z	R ¹	R ²	Yield %
127	2-chloropyrimidin-4-yl	Br	methoxy	17
128	2-chloropyrimidin-4-yl	Cl	Cl	29
129	2,6-dimethoxyphenyl	Cl	H	33
130	2,6-dimethoxyphenyl	F	F	67
131	2,6-dimethoxyphenyl	Br	H	16
132	2,6-dimethoxyphenyl	Br	F	9
133	2,6-dimethoxyphenyl	Br	methoxy	21
134	2,6-dimethoxyphenyl	Cl	Cl	15
135	2-methoxypyrimidin-4-yl	Cl	H	19
136	2-methoxypyrimidin-4-yl	Br	H	13
137	2-methoxypyrimidin-4-yl	H	methoxy	9
138	2-methoxypyrimidin-4-yl	Br	F	7
139	2-methoxypyrimidin-4-yl	Br	methoxy	9
140	2-methoxypyrimidin-4-yl	Cl	Cl	13
141	6-chloropyridazin-3-yl	Cl	H	12
142	6-chloropyridazin-3-yl	F	F	17
143	6-chloropyridazin-3-yl	Br	H	11
144	6-chloropyridazin-3-yl	H	methoxy	5
145	6-chloropyridazin-3-yl	Br	F	19
146	6-chloropyridazin-3-yl	F	methoxy	17
147	6-chloropyridazin-3-yl	Br	methoxy	3
148	6-chloropyridazin-3-yl	Cl	Cl	14
149	pyrimidin-4-yl	Cl	H	15
150	pyrimidin-4-yl	Br	H	19

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Example #	Z	R ¹	R ²	Yield %
151	pyrimidin-4-yl	Br	F	28
152	pyrimidin-4-yl	Br	methoxy	14
153	pyrimidin-4-yl	Cl	Cl	30
154	6-methoxypyrimidin-4-yl	Cl	H	8
155	6-methoxy-pyrimidin-4-yl	Br	H	6
156	6-methoxypyrimidin-4-yl	H	methoxy	6
157	6-methoxypyrimidin-4-yl	Br	F	20
158	5-cyanopyridin-2-yl	Cl	H	12
159	5-cyanopyridin-2-yl	F	F	13
160	5-cyanopyridin-2-yl	Br	H	32
161	5-cyanopyridin-2-yl	H	methoxy	2
162	5-cyanopyridin-2-yl	Br	F	23
163	5-cyanopyridin-2-yl	Cl	Cl	15
164	pyrazin-2-yl	Cl	H	22
165	pyrazin-2-yl	Br	H	12
166	pyrazin-2-yl	Br	F	16
167	6-methoxypyrazin-2-yl	F	F	20
168	6-methoxypyrazin-2-yl	Br	H	22
169	6-methoxypyrazin-2-yl	H	methoxy	11
170	6-methoxypyrazin-2-yl	Cl	Cl	14
171	6-chloropyrazin-2-yl	Cl	H	11
172	6-chloropyrazin-2-yl	F	F	25
173	6-chloropyrazin-2-yl	Br	H	15
174	6-chloropyrazin-2-yl	H	methoxy	7

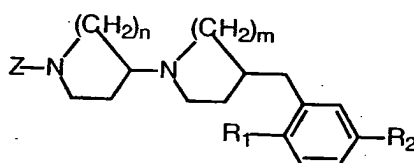
-38-

Example #	Z	R ¹	R ²	Yield %
175	6-chloropyrazin-2-yl	Br	F	13
176	6-chloropyrazin-2-yl	F	methoxy	14
177	6-chloropyrazin-2-yl	Br	methoxy	9
178	6-chloropyrazin-2-yl	Cl	Cl	21
179	5-chloro-2-methoxyphenyl	Br	F	19
180	2,4,6-trimethoxyphenyl	Br	F	23
181	6-methoxypyrazin-2-yl	Br	methoxy	4
182	pyrazin-2-yl	Cl	Cl	23
183	6-methoxypyrimidin-4-yl	Cl	Cl	11
184	6-methoxypyrimidin-4-yl	F	F	15

Additional analogs were synthesized using the aforementioned methods and were shown to inhibit the re-uptake of serotonin with $K_i < 100$ nM. Examples of these analogs are displayed in Table 2.

5

Table 2



Example #	Z	n	m	R ¹	R ²	Yield %
185	3-cyanophenyl	1	2	Br	H	37
186	3-cyanophenyl	1	2	Cl	H	26
187	2,6-dimethoxyphenyl	1	2	Cl	Cl	56
188	2,6-dimethoxyphenyl	1	2	Br	H	32

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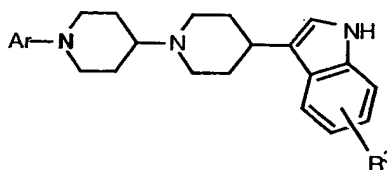
Example #	Z	n	m	R ¹	R ²	Yield %
189	2,6-dimethoxyphenyl	1	2	Cl	H	43
190	pyrimidin-2-yl	3	2	Cl	Cl	69
191	6-chloropyridazin-3-yl	3	2	Cl	Cl	65
192	6-chloropyridazin-3-yl	3	2	Br	H	29
193	pyrimidin-2-yl	3	2	Br	H	47
194	6-chloropyridazin-3-yl	2	1	Br	H	71
195	benzodioxol-5-yl	2	1	F	F	65
196	benzodioxol-5-yl	2	1	Br	H	93
197	2,6-dimethoxyphenyl	2	3	Br	H	22
198	benzodioxol-5-yl	2	3	Br	H	74
199	4,5-dimethoxy-2-methylphenyl	2	2	F	F	19
200	4,5-dimethoxy-2-methylphenyl	2	2	Br	F	21
201	4,5-dimethoxy-2-methylphenyl	2	2	Cl	Cl	15
202	2,4,6-trimethoxyphenyl	2	2	Br	H	59
203	2-methoxypyridin-5-yl	2	2	Br	H	30
204	2-methoxypyridin-5-yl	2	2	Cl	H	24
205	2-methoxypyridin-5-yl	2	2	F	F	56
206	2-methoxypyridin-5-yl	2	2	Br	F	25
207	2-methoxypyridin-5-yl	2	2	Cl	Cl	2
208	5-cyano-2-methoxyphenyl	2	2	Cl	Cl	16
209	5-cyano-2-methoxyphenyl	2	2	H	OMe	15
210	5-cyano-2-	2	2	Br	F	11

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Example #	Z	n	m	R ¹	R ²	Yield %
	methoxyphenyl					
211	2,4,5-trimethoxyphenyl	2	2	Cl	Cl	14
212	7-methoxy-2H,3H,4H-benzo[b]1,5-dioxepin-8-yl	2	2	Cl	Cl	38

Similarly, Table 3 displays examples of the indole class of compounds that were synthesized and tested and found to have K_i values < 100 nM.

Table 3



5

Example #	Ar	R ³	Yield %
213	2,3-dimethoxyphenyl	5-cyano	16
214	2,4-dimethoxyphenyl	5-fluoro	27
215	2,4-dimethoxyphenyl	5-cyano	21
216	2,5-dimethoxyphenyl	5-fluoro	27
217	2,5-dimethoxyphenyl	5-cyano	24
218	2,6-dimethoxyphenyl	5-cyano	14
219	2-chloropyrimidin-4-yl	5-cyano	14
220	2-methoxyphenyl	5-fluoro	20
221	2-methoxyphenyl	5-cyano	11
222	2-methoxypyrimidin-4-yl	5-cyano	30
223	2-methyl-benzothiazol-5-yl	5-cyano	25

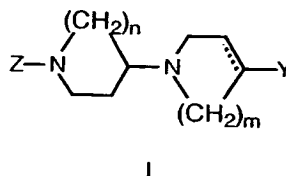
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Example #	Ar	R ³	Yield %
224	3-chloro, 4-cyanophenyl	5-cyano	16
225	3-cyanophenyl	5-fluoro	16
226	3-cyanophenyl	5-cyano	17
227	3-fluoro, 4-methoxyphenyl	5-cyano	21
228	3-fluoro, 4-methoxyphenyl	5-fluoro	8
229	4-cyanophenyl	5-fluoro	4
230	4-cyanophenyl	5-cyano	3
231	5-cyano-pyrid-2-yl	5-fluoro	22
232	5-cyanopyridin-2-yl	5-cyano	16
233	6-chloropyrazin-2-yl	5-fluoro	15
234	6-chloropyrazin-2-yl	5-cyano	7
235	6-chloropyridazin-3-yl	5-cyano	7
236	6-methoxypyrazin-2-yl	5-cyano	13
237	benzodioxan-6-yl	5-fluoro	15
238	benzodioxan-6-yl	5-cyano	20
239	benzodioxol-5-yl	5-fluoro	12
240	benzodioxol-5-yl	5-fluoro	5
241	benzothiazol-6-yl	5-cyano	2
242	pyrazin-2-yl	5-cyano	20
243	pyrimidin-2-yl	5-cyano	18
244	quinolin-5-yl	5-fluoro	5
245	quinolin-5-yl	5-cyano	27
246	quinolin-6-yl	5-cyano	12

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What is claimed is:

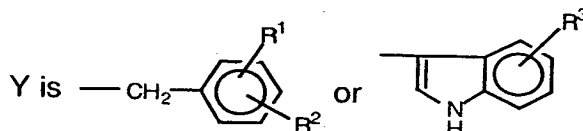
1. A compound of formula I and its pharmaceutically acceptable salts



- 5 and/or hydrates thereof wherein

Z is selected from phenyl, benzodioxolone, benzodioxole, benzothiazole, pyridine, pyridazine, pyrimidine, and quinoline moieties that are unsubstituted or optimally substituted with one to three substituents selected from C₁₋₄ alkyl, C₁₋₄ alkoxy, cyano, and halo; the solid and dotted lines denote either a double or a single covalent bond;

m and n are independently integers 1 to 3; and



in which R¹ and R² are independently selected from hydrogen, halogen or alkoxy and R³ is hydrogen, halogen or cyano.

2. The compound of claim 1 wherein Y is

3. The compound of claim 1 wherein Y is

4. A compound of claim 3 selected from
 20 1-{4-[4-(5-fluoroindol-3-yl)piperidyl]piperidyl}-2,4-dimethoxybenzene;
 3-[1-(1-(2H,3H-benzo[3,4-3]1,4-dioxan-6-yl)-4-piperidyl)4-piperidyl]indole-5-carbonitrile;

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- 3-{1-[1-(2,4-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;
3-[1-(1-(5-quinolyl)-4-piperidyl)-4-piperidyl]indole-5-carbonitrile;
3-{1-[1-(2-methylbenzothiazol-5-yl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile;
5 3-{1-[1-(2,6-dimethoxyphenyl)-4-piperidyl]-4-piperidyl}indole-5-carbonitrile.

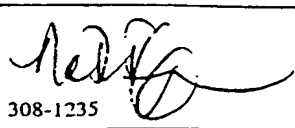
5. A compound of claim 2 selected from
5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2H-benzo[d]1,3-dioxolane;
10 5-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) quinoline;
3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) benzenecarbonitrile;
2-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl}piperidyl) pyrimidine;
2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-1,3-dimethoxybenzene;
15 3-(4-{4-[(2-bromo-5-methoxyphenyl)methyl]piperidyl} piperidyl)-6-chloropyridazine;
1-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;
1-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-
20 methylbenzene;
1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-4,5-dimethoxy-2-methylbenzene;
2-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-1,3,5-trimethoxybenzene;
5-(4-{4-[(2-bromophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
25 5-(4-{4-[(2-chlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
5-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
5-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
5-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2-methoxypyridine;
30 3-(4-{4-[(2,5-difluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;

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- 4-methoxy-3-(4-{4-[(3-methoxyphenyl)methyl]piperidyl}piperidyl)benzenecarbonitrile;
3-(4-{4-[(2-bromo-5-fluorophenyl)methyl]piperidyl}piperidyl)-4-methoxybenzenecarbonitrile;
- 5 1-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-2,4,5-trimethoxybenzene;
8-(4-{4-[(2,5-dichlorophenyl)methyl]piperidyl}piperidyl)-7-methoxy-2H,3H,4H-benzo[b]1,5-dioxepin.
- 10 6. A method for treating a patient suffering from depression comprising administration to the patient of a therapeutically effective antidepressant amount of a compound of claim 1.
- 15 7. A method for treating a patient suffering from depression comprising administration to the patient of a therapeutically effective antidepressant amount of a compound of claim 2.
- 20 8. A pharmaceutical composition comprising an antidepressant amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
9. A pharmaceutical composition comprising an antidepressant amount of a compound of claim 2 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30501

A. CLASSIFICATION OF SUBJECT MATTER IPC(7): Please See Extra Sheet. US CL: Please See Extra Sheet. According to International Patent Classification (IPC) or to both national classification and IPC														
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S.: Please See Extra Sheet. Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS--structure EAST/WEST--(serotonin or 5HT) and (uptake or reuptake)														
C. DOCUMENTS CONSIDERED TO BE RELEVANT														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
A	US 4,954,502 A (SMITH ET AL.) 04 September 1990, see entire article, especially compounds of table 1, columns 21-34.	1-9												
A, P	WO 99/32481 A1 (ALCON LABORATORIES, INC.) 01 July 1999, see entire article.	1-5, 8-9												
A, P	WO 99/51578 A1 (JANSSEN PHARMACEUTICA N.V.) 14 October 1999, see entire article.	1-5, 8-9												
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
<table border="0"><tr><td>* Special categories of cited documents:</td><td>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>*A* document defining the general state of the art which is not considered to be of particular relevance</td><td>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>*E* earlier document published on or after the international filing date</td><td>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>*A* document member of the same patent family</td></tr><tr><td>*Q* document referring to an oral disclosure, use, exhibition or other means</td><td></td></tr><tr><td>*P* document published prior to the international filing date but later than the priority date claimed</td><td></td></tr></table>			* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family	*Q* document referring to an oral disclosure, use, exhibition or other means		*P* document published prior to the international filing date but later than the priority date claimed	
* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention													
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone													
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art													
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family													
Q document referring to an oral disclosure, use, exhibition or other means														
P document published prior to the international filing date but later than the priority date claimed														
Date of the actual completion of the international search 03 APRIL 2000		Date of mailing of the international search report 02 MAY 2000												
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer CELIA CHANG  Telephone No. (703) 308-1235												

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/30501

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7): A61K 31/385, 31/445, 31/47, 31/495, 31/4995, 31/50, 31/55; C07D 215/12, 401/04, 401/14, 403/04, 403/14, 405/04, 405/14

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/212, 252, 256, 314, 318, 321, 326, 422; 540/596, 597, 602; 544/238, 333, 405; 546/176, 193, 197, 208; 548/518

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/212, 252, 256, 314, 318, 321, 326, 422; 540/596, 597, 602; 544/238, 333, 405; 546/176, 193, 197, 208; 548/518